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ADULT CELIAC SPRUE:
A LONG TERM FOLLOW-UP

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Adult Celiac Sprue:
A Long Term Follow-Up

Submitted to the Faculty of the Department of Medicine, Yale University School of Medicine, in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine.

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by: R. Michael Buckley, Jr.
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I. INTRODUCTION

During the last two decades there has been much interest and research into the childhood and adult forms of a disease characterized by malabsorbtion that investigators generally agree should now be called, as initially suggested by Rubin, (25,26) celiac sprue. Before the etiologic agent and characteristic pathological appearance were elucidated in the nineteen fifties, the highly varied presentations of malabsorbtion gave rise to many different criteria for diagnosis. This variety of opinion resulted in, at best, a highly confusing nomenclature. Synonyms for adult celiac sprue included: idiopathic steatorrhea, non-tropical sprue, idiopathic sprue, sprue syndrome, primary malabsorbtion, Gee-Thaysen disease, adult celiac disease, and gluten-induced enteropathy. (9) The childhood form of the disease was most commonly called "celiac disease".

Then, in 1950, a Dutch pediatrician (11) first suggested the use of a gluten-free diet in the childhood form of the disease, and in 1952 the gluten-free diet was introduced in adult celiac sprue. (21) This therapy has in general proven to be quite effective, (7,13,14,15) although at times unpredictable. (27) Some investigators (3,25) believe that variability in response is due to variation in the strictness of the diet; others (27) believe that this is not the case. All believe that there are some non-responders, and whether some of these

have a specific variation of the disease is being investigated. (16)

Rubin's definitive study in 1960 (22) confirmed what many investigators had long suspected; that the childhood and adult forms of celiac disease were expressions of the same basic disease process. Rubin showed that after taking peroral biopsies of the small intestine, the proximal intestinal abnormality in celiac disease and "idiopathic sprue" were identical. There is absence of villi of the duodenum and proximal jejunum in patients with celiac sprue who are eating gluten. (25) Rubin established the peroral small bowel biopsy as a necessity in the diagnosis of celiac sprue, and today celiac sprue is the most common disease diagnosed by small bowel biopsy. (29) Although the small bowel biopsy is characteristic of celiac sprue, it is not entirely specific. The other diseases with so called "flat" biopsies include: Whipple's disease, hypogammaglobulinemic sprue, Zollinger-Ellison syndrome, tropical sprue, eosinophilic gastroenteritis, kwashiorkor, and primary intestinal lymphoma. (25) Although some of these can be excluded on clinical grounds, some cannot. However, celiac sprue is the only disease with a "flat" biopsy in which the biopsy responds to a gluten-free diet. (25,29) At present, therefore, the two accepted and necessary criteria for the diagnosis of celiac sprue are the characteristic small bowel biopsy and the response to a gluten-free diet.

Clinical studies of celiac sprue since 1960 (3,7,14,20,23,27) have had the benefit of the above specific diagnostic criteria, although not all have strictly adhered to them. Nevertheless, their patient selection must certainly be considered more exact than earlier studies. Despite this, the later studies re-emphasize two characteristics of celiac sprue that earlier studies elucidated. The first is that celiac sprue presents in a wide variety of ways; some being quite subtle. The second, mentioned earlier, is that the response to a gluten-free diet is often quite variable and unpredictable. Indeed, the clinical, biochemical, and biopsy responses to the diet in the same patient seemed unrelated to one another. (3) This is often puzzling and can seemingly make it difficult to gauge the patients response to the diet.

With these thoughts in mind, it was the purpose of this study to look at the 32 patients seen at this hospital since 1960 with the diagnosis of celiac sprue, addressing ourselves to clinical observations similar to those mentioned above, and to attempt to gauge the response to a gluten-free diet in 30 of these patients. As far as was possible, an attempt was made to correlate clinical, biochemical, and pathological data in these patients, and thereby hopefully to gain some insight into the natural history of celiac sprue as we know it today.

II. MATERIALS AND METHODS

Approximately 75 charts from the Yale-New Haven Hospital and West Haven V.A. Hospital were reviewed in the spring and summer of 1971. These included all charts indexed since 1960 under both the specific diagnostic heading of "celiac sprue", (and its synonyms previously mentioned) and the broad classification of "malabsorbtion". Since this study was to be one on adult celiac sprue, it was decided to exclude all patients who had a biopsy diagnosing celiac sprue before the age of fifteen. Patients were excluded from the study who did not have biopsy proven celiac sprue. A positive response to a gluten-free diet, but without a pretreatment small bowel biopsy was not considered acceptable. Thirty-two patients were accepted into the study. Two patients had the diagnosis of celiac sprue made without biopsy and were therefore excluded. The remainder of the original seventy-five were excluded with diagnoses such as pancreatic insufficiency and Laennec's cirrhosis. Thirty of the thirty-two patients met Rubin's strict criteria (22,23,24) of a characteristic small bowel biopsy and a positive response to the gluten-free diet at some point during their follow-up. One patient, J.C., had a characteristic small bowel biopsy and a classical clinical picture but was lost to follow-up after institution of the gluten-free diet. Another patient, E.H., has a characteristic small bowel biopsy, but has been diagnosed so recently that as

this paper is being written, she is being placed on the gluten free diet. It was decided to include both of these patients in the study.

While reviewing the charts, the clinical and biochemical data collected both at the time of the initial admission, and at the various follow-up visits, was recorded. The small bowel biopsies were also reviewed. In an effort to amass as much follow-up data as possible in this group of patients, many of the patients who were being followed by various members of the department of Gastroenterology at Yale were contacted and asked if they would be re-admitted to the hospital's research ward for re-study. Seven patients consented to re-admission, and six of these to re-biopsy.

In reviewing the charts, special attention was paid to: the age and sex of the patient, the age at onset of sprue symptoms, the age at initial diagnosis, the chief complaint, the presenting symptoms and presenting physical signs. The total length of follow-up and the various clinical symptoms and physical signs at each follow-up visit were recorded.

Biochemical parameters that were looked at both at the time of presentation and during follow-up were: fecal fat (quantitative), D-xylose, serum carotene, serum iron, serum protein, serum calcium and phosphorus, alkaline phosphatase, hemoglobin, hematocrit, indices, prothrombin time and lactose tolerance tests.

An attempt was made to re-locate all of the small bowel biopsies done on the 32 patients. These numbered 75, which included the 32 done initially and a variable number of follow-up biopsies. All but 15 small bowel biopsies were found. Included in these 15 were 8 pre-treatment biopsies. The pathologists' reports on all 8 of these were found, however, and all 8 were read as "severe changes, compatible with the diagnosis of celiac sprue."

After all the charts had been reviewed and the seven patients had been re-evaluated, the clinical and biochemical data, as well as the biopsies, was "scored" in the manner described below. This was done in an attempt to quantitate the data as much as possible. This in turn served to make both clearer and more specific the correlation of the three parameters.

In all 32 patients, 4 clinical parameters were scored, however, the parameters varied from patient to patient. Most patients had one or two symptoms in common at the time of admission, for example, diarrhea and weight loss. Other symptoms, however, such as nausea or abdominal pain, would be a very crucial element in an individual patient's clinical presentation, but not appear in enough patients to allow accurate comparison. To arrive at the most accurate clinical picture it was elected to score the four parameters in each patient that were recorded most consistently in follow-up, and best represented the clinical expression of their illness.

The parameters from which the four were selected were: diarrhea, weight loss, weakness (fatigue), cramps and flatus, abdominal pain, nausea and vomiting, bleeding and purpura, and sore tongue. The first four represent the most commonly scored parameters, but the others occasionally became significant. Scores of 1 through 4 were assigned the parameters as shown in Table I.

The biochemical scoring is somewhat more accurate, because the data is, of course, quantitative to begin with. However, here a mean score had to be arrived at in each case because not only were the parameters different from patient to patient, but the number of parameters consistently followed varied widely from as few as 2 to as many as 8. The maximum number of parameters followed in each patient were scored and a mean score obtained. The biochemical parameters and their scores are listed in Table II.

The small bowel biopsies that could be relocated (see above) were looked at in a double blind fashion by two separate observers. We adopted, as did Benson,(3) a grading system after Rubin (22,23) of mild, moderate, and severe changes. We then scored normal as 1, mild as 2, moderate as 3 and severe as 4. The specific criteria of these 4 classifications and scores are presented in Table III, and in Figures I through IV.

III. RESULTS

A. Clinical Observations

Twenty-nine patients were diagnosed and followed at Yale-New Haven Hospital. Of these 17, or 57%, were women and 12, or 43%, men. There were three men diagnosed and followed at the West Haven Veterans' Administration Hospital. The age at onset of sprue symptoms, determined solely by history, the age at first biopsy diagnosis, and the duration of symptoms before diagnosis are presented in Table IV.

The three patients who had the initial onset of symptoms before age 20 had a spontaneous remission and then a relapse which brought them to medical attention and diagnosis. Twenty-two of thirty-two, or 68% of the patients, had the onset of their symptoms in the third, fourth and fifth decades. Green, in his study in 1960, (15) also found that the bulk of his patients had the onset of their symptoms between the ages of 20 and 40. Nevertheless, it is clear the symptoms of adult celiac disease may first manifest themselves at any age, and may be present for years before the patients seek medical attention. Sixty-eight per cent of the patients were diagnosed after the age of 40 and, in fact, 34% after the age of 50.

The chief complaints at the time of initial presentation to the hospital of these 32 patients are presented in Table V.

Sixty-five per cent had diarrhea as part of a chief complaint. Seventy-one per cent of the patients in this study had diarrhea

and/or weight loss as part of their chief complaint. Eighty-four per cent of the patients had the more "classical" complaints of diarrhea, weight loss, and weakness. The total array of symptoms, including the chief complaints, provided somewhat different results, and is presented in Table VI.

Ninety-four per cent of the patients had diarrhea as a symptom and 71% weight loss. Two patients did not have diarrhea. One of them, J.C., had primarily ulcer symptoms of nausea and vomiting and abdominal pain, and did, in fact, have a duodenal ulcer. The other patient, A.R., had chronic low weight and weakness, but a history of diarrhea could not be elicited. Thirty-three per cent of the patients had weakness, and 33% "cramps and gas". Twenty-nine per cent had abdominal pain, 26% faltus without cramps, and 19% had anorexia. The variety of other symptoms point out, as do the chief complaints, the number of ways that celiac sprue may present itself.

The physical signs recorded at the time of the initial physical exam are presented in Table VII. Compared to the plentitude of patients with multiple symptoms, there were few physical signs. Twenty-two per cent of the patients had increased skin pigmentation, noted primarily in the palmar creases. In two cases there was a generalized increase in skin pigmentation without exposure to the sun. In two cases the increase in skin pigmentation, in combination with other

symptoms, led to the mistaken clinical diagnosis of Addison's disease, for which the patients were initially worked up. Twenty-two per cent of the patients had a rash. In 2 patients it was diagnosed as psoriasis, in 1 seborrheic dermatitis, and in the remaining 4 no diagnosis was recorded initially. One patient, J.S., on a gluten-free diet, was subsequently diagnosed as having dermatitis herpetiformis. However, a careful review of his chart revealed a diagnosis of dermatitis herpetiformis many years before his sprue symptoms developed. Cachexia was noted in 22% of the patients. Edema of the lower extremities was present in 19%, clubbing of the fingers in 16%, and abdominal tenderness to deep palpation in 13% of the cases. Stool benzidines were positive in 14% of those patients tested. One third of the patients, however, were not tested or not recorded. Twenty-eight per cent of the patients had a normal physical exam.

B. Biochemical Results

The biochemical parameters that were recorded at the time of initial presentation to the hospital are presented in Table VIII. Of the patients tested in each category, five hour urinary D-xylose was abnormal in 93%, serum carotene in 96%, and fecal fat in 95%. Serum albumin was abnormal in 52%, and serum calcium in 46%. The electrolytes were abnormal in only one patient, M.C., and in this instance the potassium was 2.9. The hematocrit was below normal in 40% of the patients, the prothrombin time in 42%, and the serum iron was

low in 39%. Flat lactose tolerance tests occurred in 100% of those patients tested at the time of initial presentation. In three of these twelve patients glucose tolerance tests were also administered before treatment. None of the patients were diabetic. In two of the three patients the glucose tolerance tests were normal, while the lactose tolerance tests were flat, and in one both the glucose and lactose tolerance tests were flat.

C. Small Bowel Pathology

All of the small bowel biopsies, both pre and post-treatment, were reviewed in a double blind fashion by two separate observers. Of the 24 pre-treatment biopsies that were re-located, 24, or 100%, had changes of the severe type previously described.

D. Follow-up and Scoring of Data

The total length of follow-up in these 32 patients is shown in Table IX. The actual number of follow-up visits or admissions varied from patient to patient. Patients were re-biopsied at various times. Nine patients were not re-biopsied. The number of patients seen and the number biopsied at the various time intervals are shown in Table X.

The scoring method for clinical parameters has been previously described. The clinical scores at the time of initial presentation and at the various follow-up periods are given in Table XI.

Graph #1 represents the clinical scores of the 32 patients at the time of presentation and at the various follow-up periods. The solid line connects the mean clinical scores at presentation and at the various follow-up periods.

The biochemical scores at presentation, and at the various follow-up periods are shown in Table XII. These scores are plotted on Graph #2 and the solid line connects the mean biochemical scores at presentation and at the various follow-up periods.

The biopsy scores are similarly shown in Table XIII and plotted on Graph #3. The solid line again connects the mean biopsy scores at presentation and at the various follow-up periods.

Graph #4 represents the mean values of the three parameters grafted together for comparison.

IV. DISCUSSION

A. Patient Selection and Data Evaluated

With one exception that has been previously mentioned, the criteria for patient selection in this study has followed Rubin's strict guidelines. (22,23,24) Follow-up data was extensively sought after, and both data at the time of initial presentation and follow-up data, including biopsies, were carefully evaluated. The study most similar to ours is

that of Benson, Kowlessar and Sleisenger,(3) in which both the mode of presentation, and the response to follow-up, were studied. However, of the 32 patients studied by that group, only 25 had biopsy-proven celial sprue. The remaining 7 did, however, have a favorable response to a gluten-free diet. Mann, Brown and Kern's study in 1970 (20) had a biopsy-selected group of 21 patients, however, no follow-up biopsies were obtained, as they were primarily interested in the initial presentation of adult celial sprue. In 1962 Buchan studied celial disease, chosing his patients by biopsy and response to diet; this study differs from ours in that he chose to include children in his study. Shiner studied 17 patients in 1963, (27) all of whom had biopsy proven disease and were followed. He was primarily interested in their response to a gluten-free diet, and not in their manner of presentation initially. Other clinical studies (4,7,14,15,28) have reported the various ways that adult celiac disease can present and its course over time, including the response to gluten withdrawal, but did not select all their patients by either biopsy or response to diet.

B. Clinical Observations

In 1960 Green (15) found that in his 120 patients, weight loss was never a chief complaint, even though 73% of these same patients had diarrhea as their chief complaint.

In Stewart's series of 100 patients,(28) weight loss was again not mentioned as a chief complaint and, in fact, only 33% of his patients complained chiefly of diarrhea. Mann, Brown and Kern's study (20) emphasized again that adult celiac sprue may very well present in other ways than the seemingly obvious symptoms of diarrhea and weight loss. Only a total of 38% of their patients sought medical attention with chief complaints of diarrhea and weight loss. Among Benson's (3) 32 patients, however, 75% had chief complaints of diarrhea and/or weight loss. Likewise, in our study, diarrhea and weight loss are certainly the most common chief complaints, and are found in 70% of the patients. All of the studies, Benson's included, emphasize that celiac sprue patients may have a wide variety of chief complaints, a fact that became obvious in the course of our study, and is clearly evident in Table V. All of the chief complaints encountered in this study have been previously reported, (3,9,15,20,28) however, not always with the same incidence. For example, Stewart (28) reported that 33% of his patients had the chief complaint of abdominal pain, while the incidence in our study of abdominal pain as a chief complaint was only 9%. There were also symptoms reported by other investigators that were not found among our patients. These include "painful swelling of the legs" (thrombophlebitis) and tetany. (20)

In comparing Table V with Table VI it becomes obvious that there is often quite a difference between the incidence of a symptom as a chief complaint and its overall incidence as it occurs in the patients. For example, 65% of the patients had diarrhea as part of their chief complaint, while 94% of the patients had it as a symptom, and 71% of the patients had weight loss, while only 23% had weight loss as part of their chief complaint. This type of discrepancy has been reported by others. Stewart (28) found that while only 33% of his patients had diarrhea and none had weight loss as part of their chief complaint, 68% had diarrhea and 43% of his patients had, in fact, lost weight. Green (15) found similar differences. Seventy-three per cent of his patients had the chief complaint of diarrhea, while fully 90% had it as a symptom. Only 11% of his patients complained chiefly of fatigue or weakness, while 95% of the patients complained of weakness upon further questioning. None of his patients had the chief complaint of weight loss, and again, 88% had lost weight.

Graph #1 points out an equally important point. Not only do patients present with a wide variety of chief complaints and symptoms, some quite subtle, but also that patients who seek medical help and are diagnosed as having celiac sprue present in varying degrees of clinical illness. Most are moderately or severely ill at presentation, but a

range of abnormal to near-normal is present. Mann (20) points out that not only is the diagnosis often obscured by unusual and varied presenting symptoms, but also by the fact that the symptoms are often quite mild and non-specific. In addition, others (15) have found, as we did, that the onset of symptoms in adult celiac sprue is often slow and insidious.

Nine patients had normal physical examinations at presentation. In the remaining patients, findings upon physical examination at the time that they presented initially were few in number, even in patients with multiple symptoms and severe clinical disease. All of the physical signs found in this study have been previously reported, (1,3,4,5,7,10, 15,20,28) however, and when present can strengthen one's clinical assessment. An increase in skin pigmentation was one of the three most commonly encountered physical signs, and was manifested by 22% of the patients in this study. Bossak's (4) incidence of increased skin pigmentation was 11.7% and Benson's group (3) found this increase in pigmentation in 41% of their 32 patients. Twenty-two per cent of our patients were found to have skin lesions of various types previously described. Stewart (28) reports an incidence of 13% of various skin lesions in his patients, and, specifically, dermatitis herpetiformis, found in one of our patients, has been carefully studied in relation to celiac sprue. (5,6)

Clubbing of the fingers was found in 16% of our patients, which is close to the figure of 22% reported by others. (3,4) Peripheral edema was found in 36% of Bossak's (4) patients; we found the incidence to be 19%. Abdominal bloating was reported in only two patients in this study, far from the 75% incidence reported by Benson. (3) Other physical signs have been reported that were not found in our patients, but their incidence is not significant.

At this point the various complications of celiac sprue found in our patients should be mentioned. All of these complications have been previously reported.(2,3,4,5,7,9,12, 16,17,18,25) These complications, as well as illnesses found to exist concurrently with celiac sprue, often obscure the diagnosis. Such was the case with E.H., our most recent patient to be diagnosed, who like A.V., another of our patients, has diabetes mellitus. Celiac sprue is certainly not the first cause of diarrhea in a diabetic that one considers, nevertheless, she eventually came to small bowel biopsy, and the classical changes of celiac sprue were found. N.H. presented with low back pain and a history of multiple traumatic fractures in childhood. She was found to have severe osteomalacia. She had only minimal gastrointestinal symptoms. Juergens (18) found that only after careful questioning could minimal gastrointestinal symptoms be found in his patients with osteomalacia secondary to celiac sprue, and he concluded that in patients in whom the cause of osteo-

malacia is obscure, sprue should always be considered. Another patient, J.S., in whom the diagnosis of celiac sprue was initially obscure, presented with severe gastrointestinal hemorrhage secondary to malabsorbtion of vitamin K, and hypoprothrombinemia, a well known complication of celiac sprue. (18) After discharge this same patient also developed the lesions of dermatitis herpetiformis, a disease associated with celiac sprue that has been well studied. (5,6) The precise relationship of the two diseases is not clear, since neither responds to the therapy of the other. However, Brow, Rubin and their associates (5,6) believe that perhaps all patients with dermatitis herpetiformis might have a characteristic sprue biopsy, although this has not as yet been proven.

Hypogammaglobulinemia has been reported (3,9,25) as a complication of celiac sprue. Low gamma G, gamma A, and gamma M have all been found, with gamma M usually returning to normal in response to the gluten-free diet. (9) In one of our patients, D.H., severe hypogammaglobulinemia, with gamma A, G, and M all being involved, has persisted despite response of other parameters to the gluten-free diet. For this, and many other reasons, lymphoma, another known complication of celiac sprue, (17) is strongly suspected in this patient, and in fact was found in another of our patients, B.L. B.L. was also found to have another complication of celiac sprue, (2) multiple small bowel ulcers. These initially

prevented a response to the gluten-free diet, and it is occasionally this failure of response, as will be discussed subsequently, that leads to a search for, and eventual diagnosis of, complications of celiac sprue.

C. Biochemical Findings at Presentation

As demonstrated in Table VIII, a significant number of patients, though not all, were tested in each biochemical parameter. The high percentage of patients with abnormal d-xylose tests is as expected, and agrees with other reports. (10,20) Benson, however, states in his study (3) that a normal d-xylose precludes untreated adult celiac sprue. We found this not to be the case. Two of our patients had normal five hour urinary d-xylose tests and were diagnosed by biopsy as having celiac sprue and they responded to a gluten-free diet. Serum carotene was abnormal in 96% of our patients, higher than Benson's(3) incidence of 73%, but similar to Mann's (20) incidence of 93%. Although the incidence of steatorrhea has been reported as low as 65%, (20) the incidence in this study was 95% as measured by 72 hour fecal fat. Low serum albumin has been reported as high as 73% (3) and 84% (20) of patients, so it was not at all surprising to find that over half (52%) of our patients had a low serum albumin. The incidence of low serum calcium has been reported in the range of 65%,(3,4,20) our figure was again somewhat lower, 46%. Our incidence of

abnormal hematocrit, prothrombin time, and serum iron agrees with previous studies. (3,4,12,20) It has also long been known that lactose is often malabsorbed as a result of celiac sprue, and Cooke (10) reports that it often takes a long time for this defect to correct itself. All of the patients tested in this study before treatment had a flat lactose tolerance curve, however, only two had the classical symptoms of cramps, abdominal bloating, and diarrhea. Two patients were not re-tested, 7 patients had a normal curve after therapy with the gluten-free diet, and in three patients the curve remained flat, despite the fact that other parameters had returned to normal. Of these three patients, two had had the classical symptoms initially. All three were kept on a lactose-free and gluten-free diet.

Graph #2, which represents the biochemical scores of the patients, is analagous to Graph #1. It points out that the range of biochemical disease in patients with untreated celiac sprue is wide, both at presentation and during follow-up.

D. Biopsy Data at Presentation

The fact that 100% of the pre-treatment biopsies were reviewed in a double blind fashion were scored as class 4 merely re-states Rubin's definition of the pathological picture in this disease, that is, that there is a total absence of villi from 100% of patients with adult celiac

disease who are eating gluten. (25) Since this has been the criteria for diagnosis at Yale-New Haven Hospital and the West Haven V.A. Hospital, the nature of the study was such that non-flat biopsies would not be located.

E. Follow-up Data and Response to the Gluten-Free Diet

Before discussing the specific implications of the follow-up data, it must be mentioned that although every attempt was made to accurately assess the strictness of the gluten-free diet in the 30 patients followed, it was, in most cases, impossible. Sadly, in most of the charts reviewed not so much as a mention of the diet was to be found. Therefore, no significant correlation can be made between strictness of diet and level of response, as Benson has done. (4) In the patients whom we were able to contact and re-admit, careful questioning revealed that approximately one-half of the patients either occasionally or frequently strayed from the diet, sometimes knowingly and sometimes not, and simply put up with the consequences. These were usually mild diarrhea or abdominal cramps. If the indiscretions were continued, weight loss eventually resulted. The other half of the patients strictly adhered to the diet, and involuntary lapses were noted and corrected by the patients themselves. All of the patients stated that the diet was not that inconvenient, but on occasion they longed for the foods they used to eat, despite their

pre-diagnosis state of ill-health. One might, therefore, surmise that the 30 patients followed represent all levels of adherence to the diet, the strictness depending upon a wide variety of factors. Observations made and conclusions drawn about the response to the gluten-free diet will be made with the assumption that this heterogeneity is the rule in clinical practice, and will be found where the constant controls of the hospital metabolic ward are absent.

The various graphs on which are plotted the parameters of response to the gluten-free diet make several points. The first is the obvious one, shown in Graphs #1 and #2, that people on a gluten-free diet improve clinically and biochemically. They also make it clear that the "mean response" curves will not necessarily be followed in any individual case. The wide range of clinical and biochemical illness is apparent even after gluten-free diet has been instituted, showing a variability in response, with the majority of patients significantly improved. This variability in response has been observed and reported by others. (2,3,7,14,21,23,27,31) Graphs #3 and #4 emphasize that although clinically and biochemically patients can return to normal, their biopsies do not. (3,23,24,27) Assuming that the scoring system is roughly equivalent in the three parameters, it becomes obvious that the biopsies are in general more severe than one would expect from the

clinical and biochemical status of the patient, especially after the gluten-gree diet has been instituted. The general pattern of response is, however, very similar. But the graphs do not give one an accurate idea of the response to the diet in individual cases, nor do they allow any specific correlations to be made among the clinical, biochemical, and pathological parameters. Therefore, a more complete and more individualized look at the response to the gluten-free diet is seen in Table XIV.

Table XIV represents the response to the gluten-free diet in the 30 patients followed. Shiner, (27) who judged response by combining the clinical and biochemical parameters, found that 13 of his patients responded and 4 did not. Buchan, (7) who judged response in the same was as Shiner, found a good response in 32 patients, a moderate response in 4, and a poor response in 5. However, this table, and the two that follow, point out a difficulty that is encountered when speaking of the response to the diet, that is, that the clinical, biochemical, and biopsy parameters may show a very different pattern of response in the same patient. The clinical response is, in a sense, the most important, for if the patient is normal by biochemical measurements, and has a good biopsy response, but is clinically very ill, then that patient must be carefully re-evaluated. There were 2 patients in this study who did not respond at all clinically. The first, R.J., also had

no biochemical or biopsy response. The patient died of pneumonia, and at autopsy, in addition to celiac sprue, was found to have a large ulcer at the gastro-esophageal junction, epidermoid carcinoma of the lung, and two large lung abscesses. In the second patient, B.L., multiple small bowel ulcers, a known complication of celiac sprue, (2) were found at laparotomy. Before this she had had essentially no clinical response, although her malabsorbtion parameters were never significantly abnormal, and her follow-up biopsy showed only mild changes.

The extent and range of the biochemical and biopsy response in the 28 patients who did respond, at least moderately well, to the gluten-free died is shown in Table XV. Looking at Table XV, one wonders whether any prediction could ever be made about a patient's response to diet in any given parameter, knowing the results of one, or even two, parameters in advance. Table XVI, represents a comparison of the three parameters looked at in this study in the 9 patients that were the most thoroughly studied in all three parameters simultaneously. The table can be used to point out possible correlations between parameters, and when, if possible, one might predict from one parameter what another might be.

The conclusions that can be drawn from this table are consistent in all 30 patients followed. The first is that if a patient is clinically severely ill, that is, the

patient's mean clinical score is 3.0 or greater, that patient's biochemical and biopsy picture will be moderate or severe, and not mild. There is one exception to this rule, #29, B.L., who had small bowel ulcers complicating her sprue. Her clinical score was severe due to abdominal pain and nausea and vomiting, due most probably to her ulcers; while her malabsorbtion parameters and her small bowel biopsy showed that her sprue was mild, and thus the discrepancy. No other patients who were severely ill clinically had mild disease by biochemical measurement or by biopsy.

The second prediction that can be made is that if the patient by biochemical measurements is moderately to severely ill, that is, a score of 2.5 or greater, that patient's biopsy will show moderate or severe, and never mild, changes. Among the biopsies that were available we found no exceptions to this.

The converse of the above two statements, however, is not true, nor could any other correlations or predictions be made. If the patient is severely ill biochemically, he might be mild, moderate or severely ill clinically. If the patient had a moderate or severe biopsy, that patient might be mildly, moderately, or severely ill clinically, biochemically or both. Often we found severe changes on biopsy in the face of clinically and biochemically mild disease. Whether this is related to the length of intestine involved,

as Rubin and others suggest, (3,23,24,26) we were unable to determine, although this certainly seems a likely explanation. In fact, there are many questions about celiac sprue that remain unanswered, a fact that makes the disease all the more fascinating. For example, assuming that the disease is inherited, or at least the pathological small bowel lesions, what in fact are the trigger mechanisms which allow the disease to become clinically manifest over such a wide range of ages? That is, in two people with the same small bowel lesion, why should one have symptoms at age 25 and the other not until age 60?

It is known that celiac sprue may become clinically evident during the stress of pregnancy and following abdominal surgery such as gastrectomy, but the vast majority of trigger events are only speculated, and the question of sub-clinical disease remains very puzzling. It has also been shown that in families that have been studied one member may have clinical disease while other family members have the characteristic biopsy and have never had symptoms! Why one exacerbates at any given time and another does not may in some way be related to the lack of correlation between biopsies and clinical symptoms in patients with clinical disease, that is, a severe biopsy associated with mild biochemical and clinical illness.

This study by no means answers any of these questions, but merely re-emphasizes them. Perhaps when the precise

etiology of this disease is determined many of these questions about celiac sprue will no longer remain unanswered.

Table I

Scores of Eight Clinical Parameters of Celiac Sprue

Diarrhea:	1 - 2 stools	1
	3 - 5 stools	2
	6 - 10 stools	3
	greater than 10	4
Weight Loss:	0 - 4 pounds	1
	5 - 10 pounds	2
	10 - 20 pounds	3
	greater than 20	4

Weakness (fatigue), cramps and flatus, abdominal pain, nausea and vomiting, bleeding and purpura, and sore tongue were scored in the following manner:

mentioned as "not present", or "normal"	1
mentioned as "present", or "abnormal"	2.5
patient's chief complaint or specifically recorded as "very severe" or "4+"	4

Range of Total Scores	4 - 16
Range of "mean" Scores	1 - 16

Table II

Scores of Nine Biochemical Parameters of Celiac Spruce

d-xylose (5 hour urine) (grams)	greater than 4.5	1
	2.5 - 4.5	2
	1.5 - 2.4	3
	less than 1.5	4
Fecal fat (24 hour) (grams)	less than 6	1
	6 - 10	2
	11 - 29	3
	greater than 29	4
Carotene (serum) (ug%)	70 - 200	1
	50 - 69	2
	25 - 49	3
	less than 25	4
Albumin (serum) (gm%)	greater than 3.4	1
	3.0 - 3.4	2
	2.5 - 2.9	3
	less than 2.5	4
Calcium (serum) (mg%)	greater than 9.1	1
	8.5 - 9.0	2
	7.5 - 8.4	3
	less than 7.5	4

Table II

(Continued)

Hematocrit (Male) (%)	greater than 39	1
	35 - 39	2
	30 - 34	3
	less than 30	4
Hematocrit (Female) (%)	greater than 37	1
	32 - 37	2
	28 - 31	3
	less than 28	4
Iron (serum) (Male) (ug%)	60 - 180	1
	50 - 59	2
	40 - 49	3
	less than 40	4
Iron (serum) (Female) (ug%)	50 - 170	1
	40 - 49	2
	30 - 39	3
	less than 30	4

Maximum mean score ... 4

Minimum mean score ... 1

Table III

Scoring of the Small Bowel Biopsies

Score= 1:	Normal - villi tall, slender, and uniform in size and shape, villus/crypt ratio 3/1 or greater. Epithelial cells have clear cytoplasm and are columnar, with nuclei placed regularly at the cell base. Brush border is uniformly thick. Round cells are present in the lamina propria, but are not concentrated there. (See Figure I)
Score= 2:	Mild changes - villi are formed, but are somewhat broader and shorter than normal. The villi and the villus/crypt ratio often approach normality. However, epithelial cells, especially at the tips of the villi, are still abnormal, often the nuclei are not basally located, and the cells themselves are not as tall and columnar as in the normal biopsy. Round cells are present in an increased concentration in the lamina propria. The brush border has usually returned to normal, except, again, at the very tips of the villi. (See Figure II)

Table III
(Continued)

Score= 3: This group encompasses the wide range between mild and severe. Villi are present, but they are broad and short. Epithelial cells are not yet columnar, and their nuclei are disoriented, but less so than in class 4. The round cell infiltrate is dense, but again less so than in the severe biopsy. The villus/crypt ratio is often still less than 1. (See Figure III)

Score= 4: Complete absence of villi, or, at best, very short and very broad. There is flattening of the mucosal surface, with absence and irregularity of the brush border. The epithelial cells themselves are columnar, often vacuolated, and have nuclei scattered anywhere from the base of the cell to the tip. The villus/crypt ratio is less than 1 and often is 1/3 or less. There is an obvious increase in mitotic figures in the crypts. There is a dense infiltrate in the lamina propria of chronic inflammatory cells. (See Figure IV)

Table IV

Age Factors and Duration of Symptoms before Diagnosis in Celiac Sprue

Age Groups	Number of patients at onset of symptoms	Number of patients at time of diagnosis
Childhood	1	-
15-19 yrs.	2	-
20-29 yrs.	9	5
30-39 yrs.	6	5
40-49 yrs.	7	11
50-59 yrs.	4	6
60-69 yrs.	3	5

Duration of Symptoms	Number of Patients
1 week - 11 weeks	2
3-6 months	6
1-2 years	6
3 years	4
6 years	3
10-15 years	5
greater than 15 years	6

Table V

Chief Complaint at Time of Initial Presentation

Diarrhea alone - 10 patients
Diarrhea & weight loss - 6 patients
Diarrhea, nausea and vomiting - 2 patients
Diarrhea & fatigue - 1 patient
Diarrhea & flatus - 1 patient
Diarrhea & abdominal pain - 1 patient

DIARRHEA
21 patients

Weight loss alone - 1 patient
Weight loss and increased pigmentation - 1 patient
Weakness - 1 patient
Fatigue - 1 patient
Sore tongue - 1 patient
Abdominal pain, nausea and vomiting - 2 patients
Swelling of legs - 1 patient
Difficulty walking - 1 patient
Low back pain - 1 patient

Total - 32 patients

Table VI

Symptoms at Time of Initial Presentation of 32 Patients with Adult Celiac Sprue

Diarrhea - 30 patients

Weight Loss - 23 patients

Weakness - 11 patients

"cramps and gas" - 10 patients

Abdominal pain - 9 patients

Flatus - 8 patients

Anorexia - 6 patients

Abdominal distention - 5 patients

Muscle cramps - 4 patients

Bone pain - 4 patients

Peripheral edema - 4 patients

Nausea and vomiting - 3 patients

Fatigue - 3 patients

Purpura - 2 patients

Sore tongue - 2 patients

Paresthesias - 2 patients

Rectal incontinence - 2 patients

Increased skin pigmentation - 2 patients

Joint pain - 1 patient

GI bleeding - 1 patient

Nose bleeding - 1 patient

Table VII

Physical Signs at Initial Presentation of 32 Patients with Adult Celiac Sprue

Increased skin pigmentation - 7 patients

Rash - 7 patients

Cachexia (or muscle wasting) - 8 patients

Peripheral edema - 6 patients

Clubbing - 6 patients

Abdominal tenderness - 4 patients

Pale conjunctiva - 3 patients

Abdominal distention - 2 patients

"arthritis" - 1 patient

Lymphadenopathy - 1 patient

Bleeding (nose) - 1 patient

Hyperactive bowel sounds - 2 patients

Stomatitis - 1 patient

Palpable loops - 1 patient

Hepatomegaly - 1 patient

Stool Benzidine - positive - 3 patients
negative - 18 patients

Normal physical exam - 9 patients

Table VIII

Biochemical Abnormalities at Initial Presentation of 32 Patients with Adult Celiac Sprue

	Number of Patients Abnormal	Number of Patients Tested	Definition of Abnormal
D-xylose	25/27		less than 4.5 grams
Carotene	28/29		less than 70 ug%
Fecal fat (24 hour)	20/21		greater than 6 grams
Albumin	16/30		less than 3.4 gm%
Calcium	13/28		less than 9.1 mg%
Iron	7/18		less than 60 ug% (male) less than 50 ug% (female)
Electrolytes	1/32		Na less than 34mEq/L HCO_3 less than 25.1 mEq/L K+ less than 3.6 mEq/L Cl less than 100 mEq/L
Hematocrit	12/32		less than 40% (male) less than 38% (female)
Prothrombin time	12/27		less than 100%
Lactose tolerance test	12/12		"flat"

Table IX

Total Length of Follow-up in 32 Patients with Adult Celiac Sprue

Length of Follow-up	Number of Patients
None	2
3-6 months	4
9-12 months	7
2 years	2
3 years	6
4 years	5
5 years	3
6 years	2
8 years	1

Table X

Number of Patients Followed at Various Time Intervals

Time Intervals	Number of Patients followed Clinically and/or Biochemically	Number of Patients Biopsied
Presentation	32	32
3-6 months	21	14
9-12 months	15	8
2 years	7	7
3 years	5	2
4 years	7	4
5 years	2	1
6 years	2	2
8 years	1	0

Table XI

Clinical Scores of 32 Patients with Adult Celiac Sprue

Maximum Score = 16 (severe symptoms)

Minimum Score = 4 (normal - no symptoms)

		Presentation	3-6mo.	9-12mo.	2yrs	3yrs	4yrs	5yrs	6yrs	8yrs
#1	D.H.	13	10	5	4		4	7		
#2	M.S.	11	4	4			4			
#3	J.C.	9								
#4	E.M.	15	6		11		11			
#5	S.C.	12	11							
#6	D.M.	14	4	4						
#7	N.H.	7		5	5		6			
#8	R.L.	8	4			5				
#9	R.J.	16	11			14				
#10	A.V.	12		4			5			
#11	L.W.	12	4	4						
#12	E.P.	12	5			5				
#13	E.I.	6				4				
#14	A.R.	8		4						
#15	M.C.	14	4	5						
#16	H.L.	6			5					5
#17	J.W.	13	7	6						
#18	M.H.	11	5	5					7	

Table XI

(Continued)

	Presentation	3-6mo.	9-12mo.	2yrs	3yrs	4yrs	5yrs	6yrs	8yrs
#19 J.S.	14	5							
#20 M.C.	10	4							
#21 J.D.	14	7	4						
#22 W.H.	11	4		4			5		
#23 P.C.	9	5		5		5	5		
#24 C.S.	7	4	4						
#25 J.T.	11	4	4	4		4			
#26 L.L.	11	4							
#27 A.H.	12			6					
#28 M.H.	12			12	10				
#29 B.L.	14	14	14						
#30 J.N.	12	7	5						
#31 R.W.	9	4	4						
#32 E.H.	12								

Table XII

Biochemical Scores of 32 Patients with Adult Celiac Sprue

Maximum Score = 4 (severe)

Minimum Score = 1 (normal)

		Presentation	3-6mo.	9-12mo.	2yrs	3yrs	4yrs	5yrs	6yrs
#1	D.H.	3.8	3.2	3.2	2.5		2.3		
#2	M.S.	3.2	2.5		1.7				
#3	J.C.	3.2							
#4	E.M.	3.5							
#5	S.C.	3	1.6						
#6	D.M.	2.6	2	1					
#7	N.H.	1.6	1	1	1.3		1.3		
#8	R.L.	2.6	1.3			1			
#9	R.J.	3.6	3			3			
#10	A.V.	3.2		1.3			1.2		
#11	L.W.	3.7	1	1					
#12	E.P.	2.5	1			1.7			
#13	E.I.	2						3.3	
#14	A.R.	3		1					
#15	M.C.	3.5	1.3	1.2					
#16	H.L.	2		2	2	1			
#17	J.W.	4	4	4					
#18	M.H.	3	1	1					

Table XII

(Continued)

	Presentation	3-6mo.	9-12mo.	2yrs	3yrs	4yrs	5yrs	6yrs
#19 J.S.	3.3							
#20 M.C.	3	1.3						
#21 J.D.	2.7	1	1					
#22 W.H.	4	2		1			1	
#23 P.C.	2.5	1		1		1		1
#24 C.S.	2	1				1		
#25 J.T.	3.1	1.3	1	1		1		
#26 L.L.	3	1.2						
#27 A.H.	2.7			3.3				
#28 M.H.	3.2	3.0			3.8			
#29 B.L.	1.7	1.8	1					
#30 J.N.	3.2	1.3						
#31 R.W.	3.2	1	1					
#32 E.H.	3.4							

Table XIII

Biopsy Scores in 32 Patients with Adult Celiac Sprue

4 = severe
2 = mild
3 = moderate
1 = normal
X = could not find

		Presentation	3-6mo.	9-12mo.	2yrs	3yrs	4yrs	5yrs	6yrs
#1	D.H.	4	3	4	X				
#2	M.S.	X					X		
#3	S.C.	4							
#4	E.M.	X							
#5	S.C.	4	2						
#6	D.M.	4							
#7	N.H.	X	4,4	3	3	3	2		
#8	R.L.	X	2	2					
#9	R.J.	4	X			X			
#10	A.V.	4		3					
#11	L.W.	X	X	2					
#12	E.P.	4	2	X					
#13	E.I.	4							
#14	A.R.	4							
#15	M.C.	X		4					
#16	H.L.	4							
#17	J.W.	4		4					
#18	M.H.	4	3		3				2

Table XIII

(Continued)

	Presentation	3-6mo.	9-12mo.	2yrs	3yrs	4yrs	5yrs	6yrs
#19 J.S.	4							
#20 M.C.	4	3						
#21 J.D.	4							
#22 W.H.	4	3,2		2			3	
#23 P.C.	4			3		3		3
#24 C.S.	4	2				2		
#25 J.T.	X			2				
#26 L.L.	4	3						
#27 A.H.	4			4				
#28 M.H.	4			3	4			
#29 B.L.	X					2		
#30 J.N.	4	3						
#31 R.W.	4	X						
#32 E.H.	4							

Table XIV

Response to the Gluten-Free Diet in 30* Patients with Adult Celiac Sprue

(judged at time of last follow-up)

A. Clinical

good response - (score 4-7)	25 patients
moderate response - (score 8-11)	3 patients
poor response - (score 12-16)	2 patients

B. Biochemical

good response - (score 1-1.9)	22 patients
moderate response - (score 2.0-2.9)	1 patient
poor response - (score 3.0 - 4.0)	5 patients

C. Biopsy

good response - (score 2)	9 patients
moderate response - (score 3)	6 patients
poor response (none) - (score 4)	5 patients

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* As was mentioned, two of the patients were not followed after initial diagnosis.

Table XV

Biochemical and Biopsy Response in 28 Clinical Responders to the Gluten-Free Diet

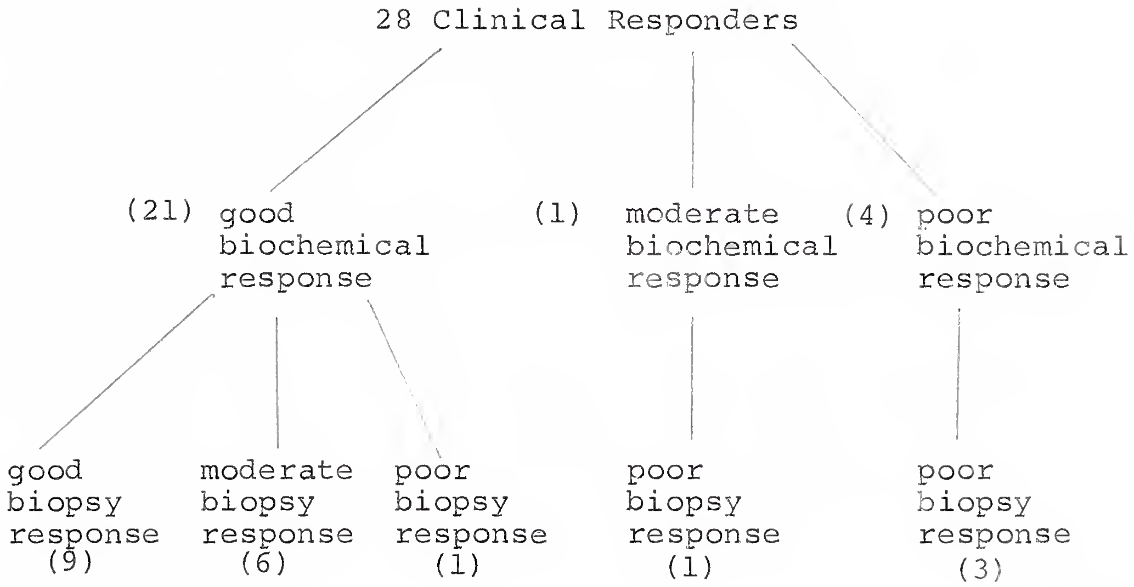

28 Clinical Responders
(21) good biochemical response
(1) moderate biochemical response
(4) poor biochemical response
good biopsy response (9)
moderate biopsy response (6)
poor biopsy response (1)
poor biopsy response (1)
poor biopsy response (3)

Table XVI

Clinical, Biochemical and Biopsy Parameters in Nine Patients with Celiac Sprue

	Scores		
	Clinical	Biochemical	Biopsy
#1 D.H.			
Presentation	3.2	3.8	4
3-6 months	2.5	3.8	3
1 year	1.2	3.2	4
#7 N.H.			
Presentation	1.7	1.6	4
3-6 months		1	4
9-12 months	1.2	1	3
2 years	1.2	1.3	3
3 years	1.2	1.3	3
4 years	1.5	1.3	3
#15 M.C.			
Presentation	3.5	3.5	4
3-6 months	1	1.3	
1 year	1.2	1.2	4

Table XVI

(Continued)

	Scores		
	Clinical	Biochemical	Biopsy
#17 J.W.			
Presentation	3.2	4	4
3-6 months	1.7	4	
1 year	1.5	4	4
#22 W.H.			
Presentation	2.2	4	4
3-6 months	1.2	2	3
2 years	1.2	1	2
4 years	1.2	1	3
#23 P.C.			
Presentation	2.3	2.5	4
2 years	1.2	1	3
4 years	1.2	1	3
6 years	1.2	1	3
#27 A.H.			
Presentation	3	2.7	4
2 years	1.5	3.3	4

Table XVI

(Continued)

	Scores		
	Clinical	Biochemical	Biopsy
#28 M.H.			
Presentation	3	3.2	4
3-6 months	3	3.0	3
3 years	2.5	3.8	4
#29 B.L.			
Presentation	3.5	1.7	
3-6 months	3.5	1.8	
4 years	3.5	1	2

Legend for Graphs

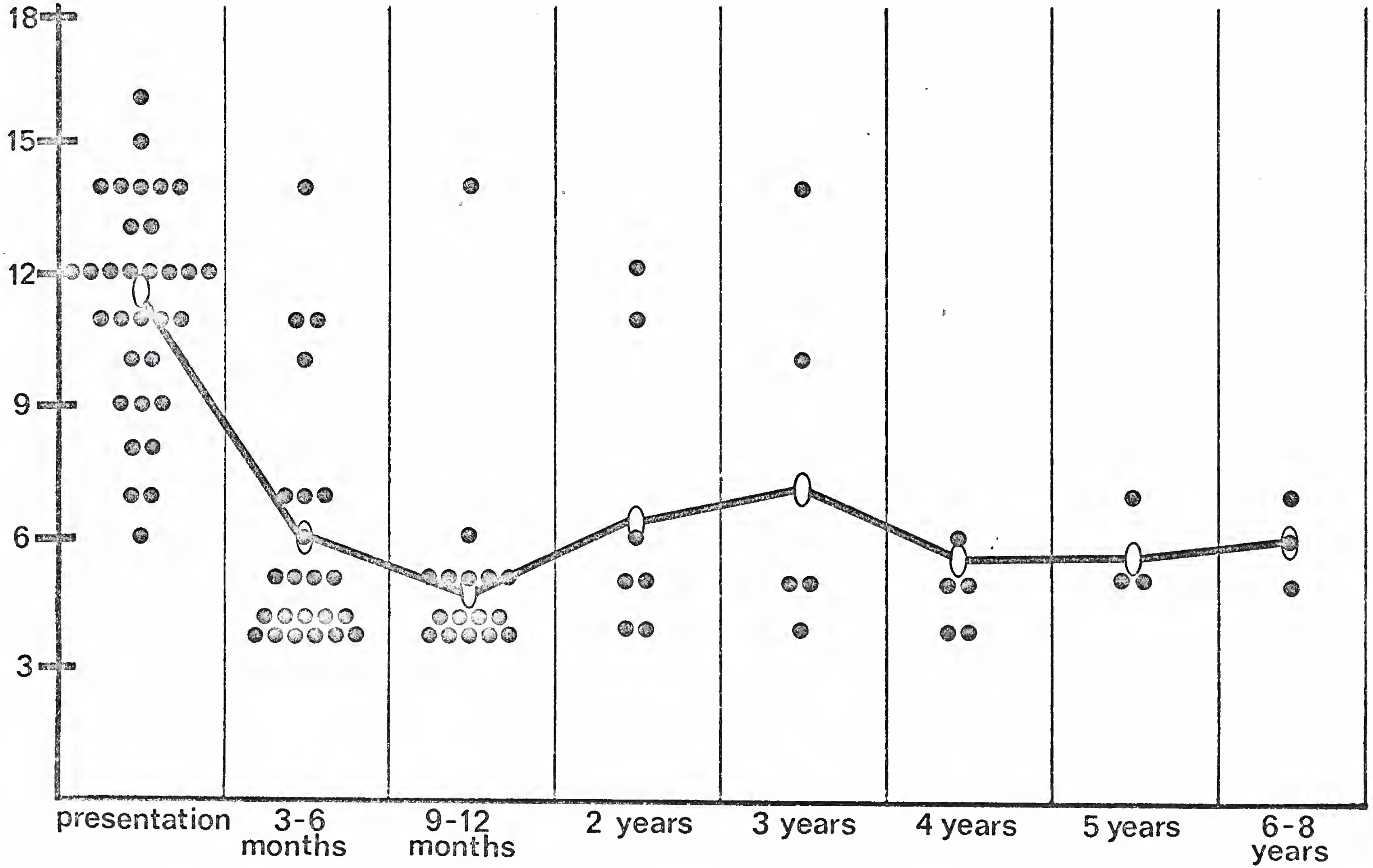
Graph #1 represents the clinical scores of the 32 patients at the time of presentation, that is, the time the patient was initially diagnosed by biopsy, and at the various follow-up periods. The solid line connects the mean clinical score at presentation to the mean scores at the various follow-up periods.

Graph #2 represents the biochemical scores of the 32 patients at the time of initial presentation, and at the various follow-up periods. The solid line connects the mean biochemical score at presentation to the mean scores at the various follow-up periods.

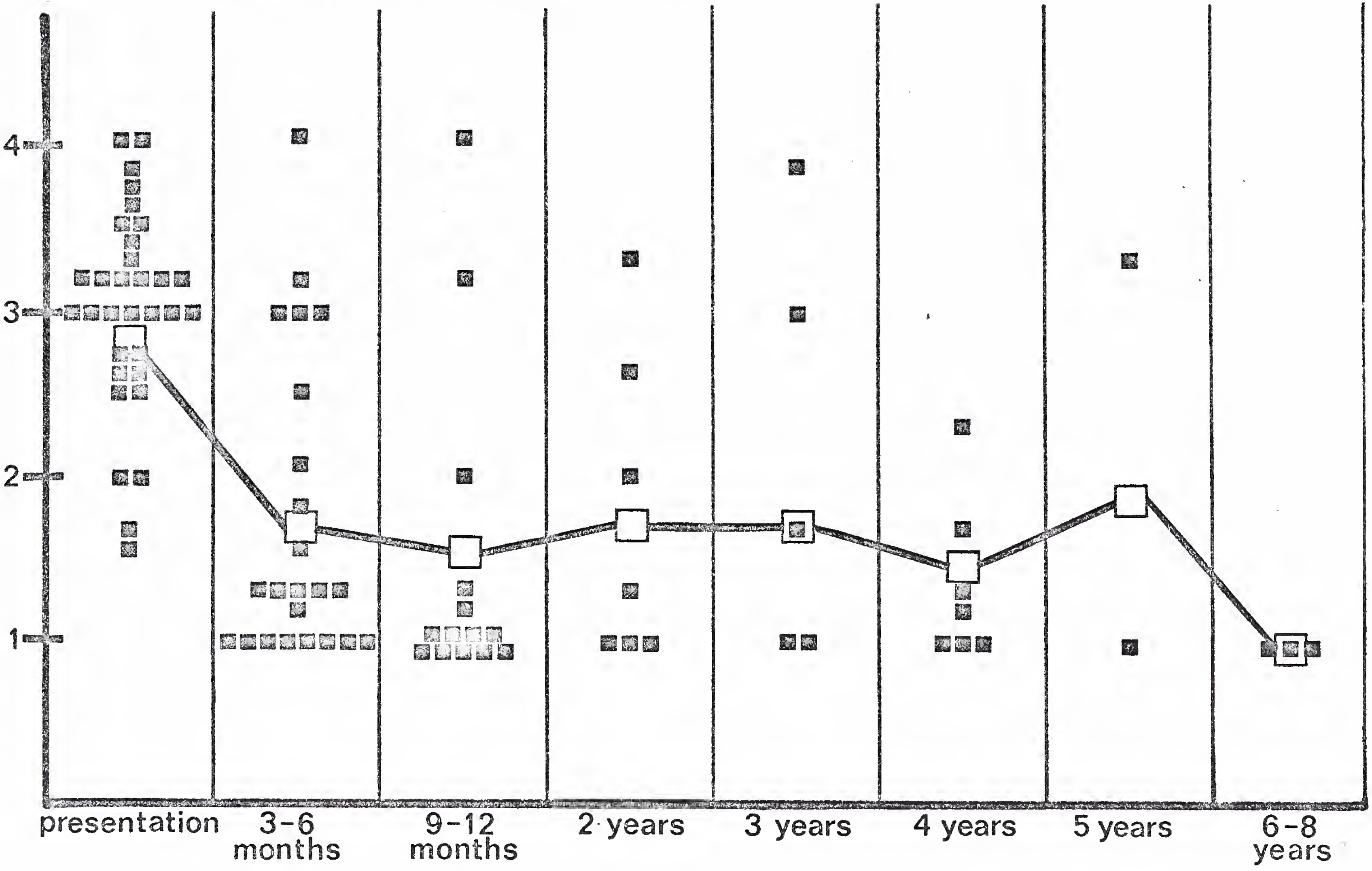
Graph #3 represents the biopsy scores of the 32 patients at the time of initial presentation, and at the various follow-up periods. The solid line connects the mean biopsy score at presentation to the mean scores at the various follow-up periods.

Graph #4 represents the mean values of the three parameters, clinical, biochemical and biopsy, grafted together for comparison.

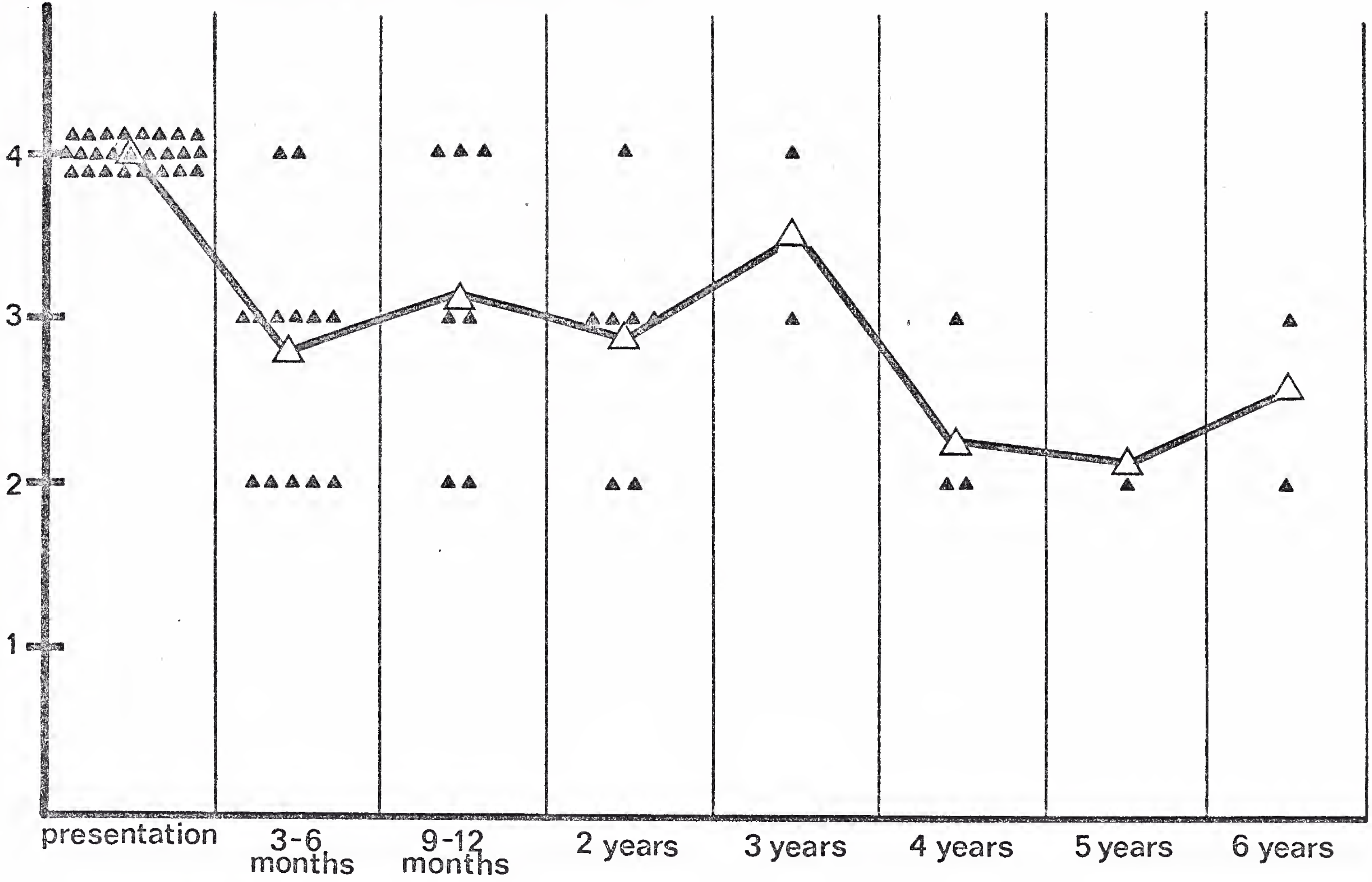
Graph 1.
Summary of clinical parameters



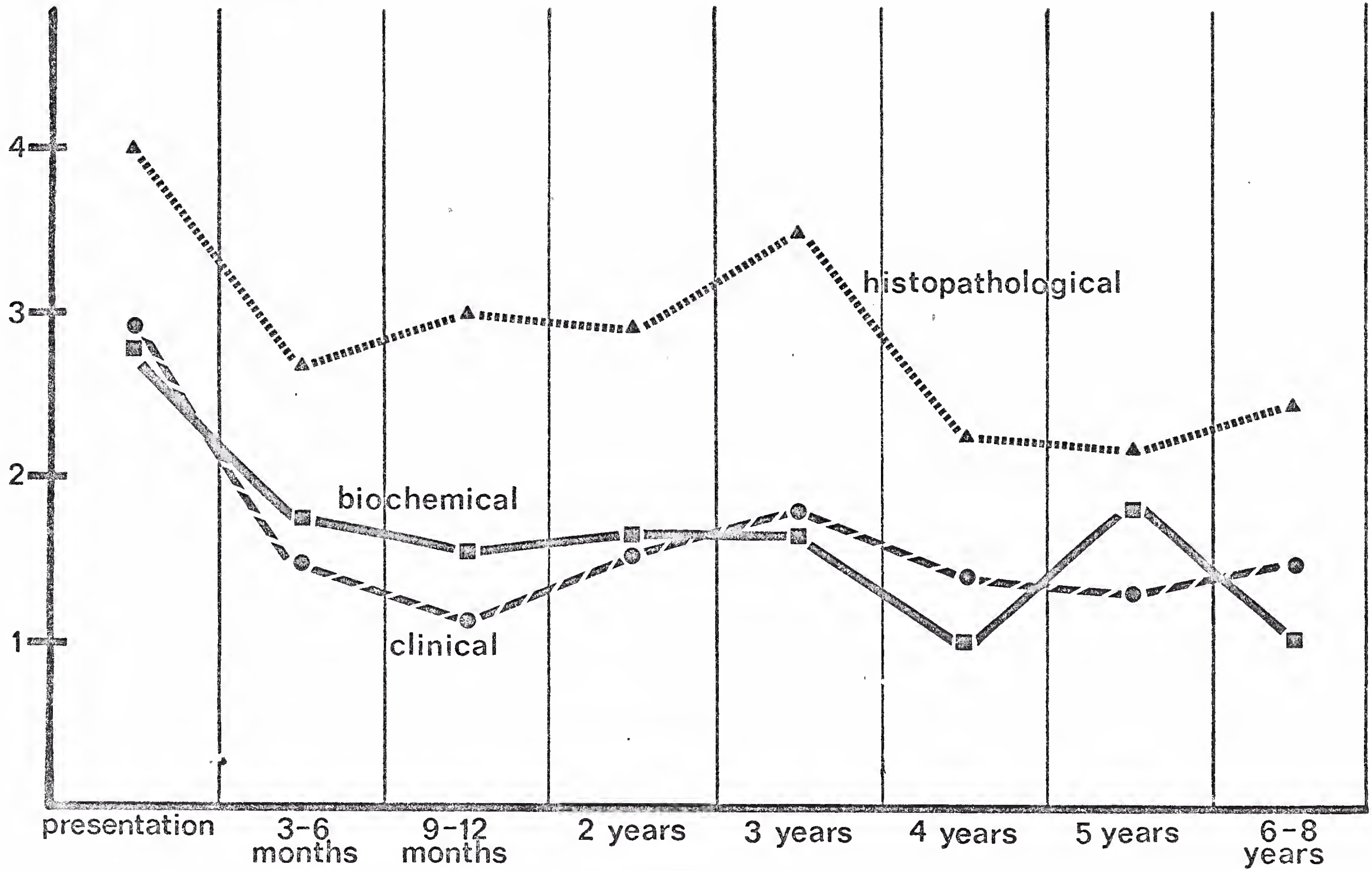
Graph 2.
Summary of biochemical parameters



Graph 3.
Summary of histopathology



Graph 4.


4
3
2
1
histopathological
biochemical
clinical
presentation
3-6 months
9-12 months
2 years
3 years
4 years
5 years
6-8 years

Legend for Figures

Figure 1 - Normal: villi tall, slender, and uniform in size and shape, villus/crypt ratio 3/1 or greater. Epithelial cells have clear cytoplasm and are columnar, with nuclei placed regularly at the cell base. Brush border is uniformly thick. Round cells are present in the lamina propria, but are not concentrated there.

Figure 2 - Mild changes: villi are formed, but are somewhat broader and shorter than normal. The villi and the villus/crypt ratio often approach normality. However, epithelial cells, especially at the tips of the villi, are still abnormal, often the nuclei are not basally located, and the cells themselves are not as tall and columnar as in the normal biopsy. Round cells are present in an increased concentration in the lamina propria. The brush border has usually returned to normal, except, again, at the very tips of the villi.

Figure 3 - This group encompases the wide range between mild and severe. Villi are present, but they are broad and short. Epithelial cells are not yet columnar, and their nuclei are disoriented, but less so than in Figure 4. The round cell infiltrate is dense, but again, less so than in the severe biopsy. The villus/crypt ratio is often still less than 1.

Legend for Figures

(continued)

Figure 4 - Complete absence of villi, or, at best, very short and very broad. There is flattening of the mucosal surface, with absence and irregularity of the brush border. The epithelial cells themselves are columnar, often vacuolated, and have nuclei scattered anywhere from the base of the cell to the tip. The villus/crypt ratio is less than 1 and often is 1/3 or less. There is an obvious increase in mitotic figures in the crypts. There is a dense infiltrate in the lamina propria of chronic inflammatory cells.

Figure 1

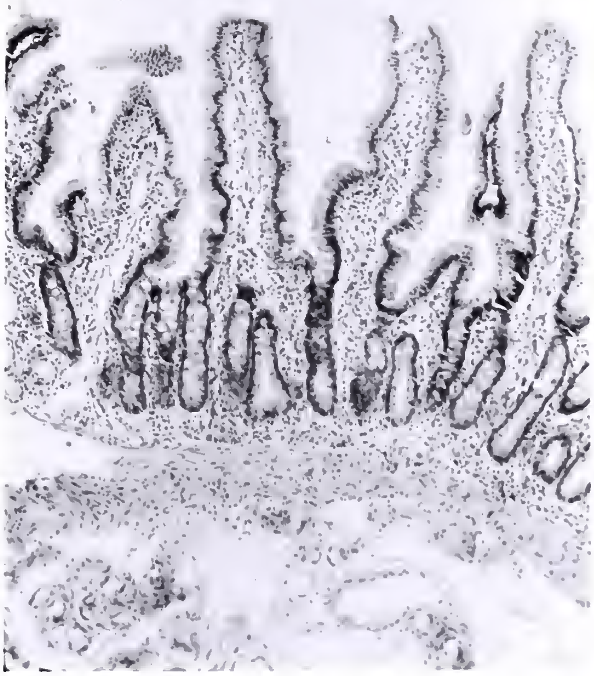


Figure 2

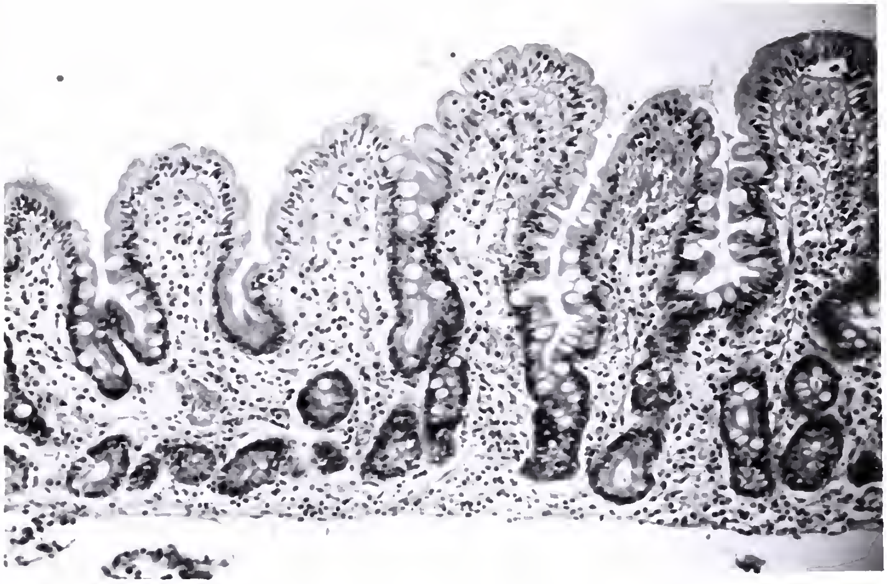


Figure 3

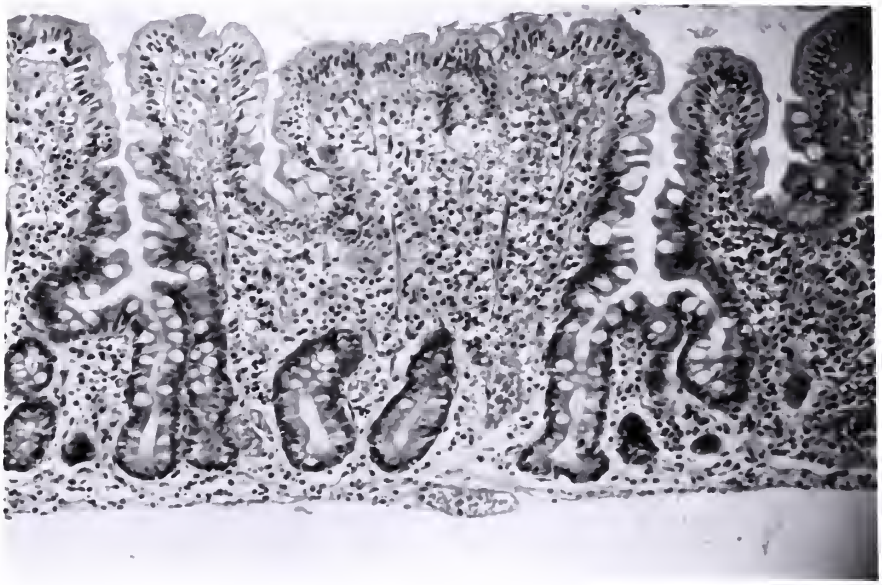
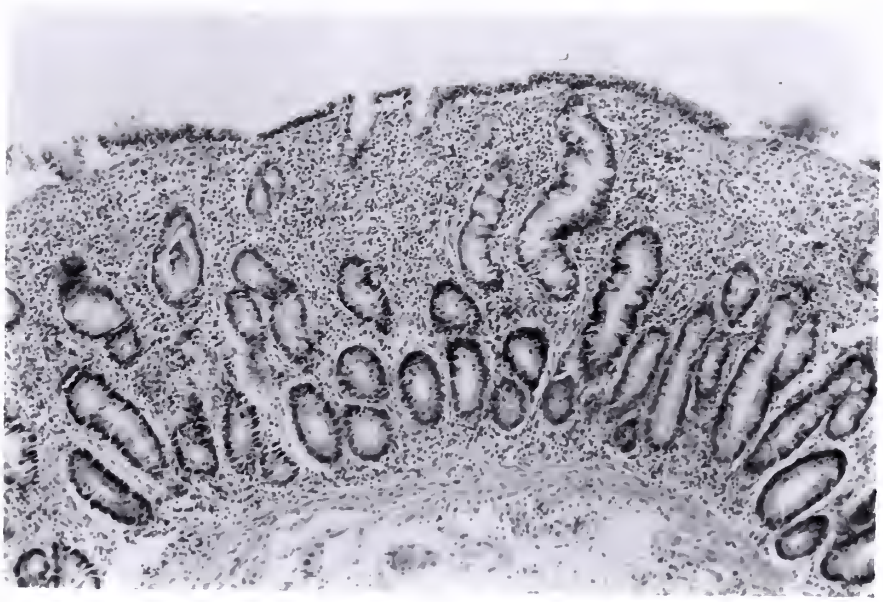


Figure 4



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